

Long-Range Chromatin Contacts in Embryonic Stem Cells Reveal a Role for Pluripotency Factors and Polycomb Proteins in Genome Organization.

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Public Summary:

Each cell within an individual's body contains the same complement of DNA, coding for the same genes. Despite their genomic uniformity, cells manage to exhibit an impressive variety of forms and functions that go into producing all the tissues of the human body. These differences are achieved through the regulation of individual genes such that they are only on in particular cell types. For instance, the regulation of specific genes allows skin cells to serve their specialized epidermal function. Embryonic stem cells (ESCs), on the other hand, have not committed to a particular cell fate and retain the ability to become one of the 200-odd types of specialized cell. This capacity to develop into any cell type is termed 'pluripotency.' Different cell types, along with turning different genes on and off, organize those genes in the three dimensional (3D) space of the cell nucleus in different configurations. Our current work demonstrates that mouse ESCs have an ESC-specific 3D genome organization, which differs from that of non-pluripotent cell types. Induced pluripotent stem-like cells, which can be generated from specialized cells such as skin cells, successfully re-establish an ESC-like genome organization. This provides further evidence that these medically promising pluripotent cells are in fact ESC-like. Additionally, we find that the ESC genome is organized in such a way as to juxtapose regions of DNA that show similar regulation by demonstrating that spatially associated regions in the genome are associated with the same gene regulatory factors. In other words, the nucleus appears to be compartmentalized into functionally related regions. This finding adds a new dimension to our understanding of how ESC-specific gene regulation is maintained and how the genome is organized.

Scientific Abstract:

The relationship between 3D organization of the genome and gene-regulatory networks is poorly understood. Here, we examined long-range chromatin interactions genome-wide in mouse embryonic stem cells (ESCs), iPSCs, and fibroblasts and uncovered a pluripotency-specific genome organization that is gradually reestablished during reprogramming. Our data confirm that long-range chromatin interactions are primarily associated with the spatial segregation of open and closed chromatin, defining overall chromosome conformation. Additionally, we identified two further levels of genome organization in ESCs characterized by colocalization of regions with high pluripotency factor occupancy and strong enrichment for Polycomb proteins/H3K27me3, respectively. Underlining the independence of these networks and their functional relevance for genome organization, loss of the Polycomb protein Eed diminishes interactions between Polycomb-regulated regions without altering overarching chromosome conformation. Together, our data highlight a pluripotency-specific genome organization in which pluripotency factors such as Nanog and H3K27me3 occupy distinct nuclear spaces and reveal a role for cell-type-specific gene-regulatory networks in genome organization.

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